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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/429,331	10/28/1999	LISA A. PAIGE	PAIGE=1D	5796

1444 7590 06/15/2005

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 06/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/429,331	PAIGE ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *135-157* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *135-157* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 135-157 are pending and under examination.

Withdrawn Rejection and Objection

The objection to the specification is withdrawn in view of the new abstract and Seq. ID. Nos. provided in the specification. The 112, second paragraph rejection is withdrawn in view of the new claims of record. Also, 101 double patenting rejection over USP 6,617,114 ('114 Patent) and the provisional obviousness double patenting over applications 09/860,688; 10/332,708. These applications have been abandoned. The 102 rejections over Kauvar and Klein are withdrawn in view of the new claims and applicants' arguments.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112, first paragraph

New claims 135-140, 142-146, 148-153 and 156 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application

was filed, had possession of the claimed invention for reasons advanced in the last Office action.

Response to Arguments

Applicants submit the specification provides full details of the definition of the panel (page 43 line 6 to page 45 line 15), reference ligands (page 41 line 15 to page 42 line 5) reference conformations (page 31 line 17 to page 32 line 9 and page 42 lines 6-25), reference fingerprint (page 45 lines 36-39), test substances (page 39 line 30 to page 41 line 15), binding assays (page 59 line 4 - page 74 line 26) and the various types of libraries used in the method (pages 92-95). Applicants further submit that clear examples have been carried out and are disclosed in the specification of the present application. Attention is drawn to the different Examples in the specification. Example 1.1 on page 130, which discloses the identification of peptides that bind to unliganded ER-alpha with specific examples listed in Table 1. Additionally, Example 1.2 and page 130 discloses different peptides that bind estradiol activated ER-alpha. This experiment allowed the identification of the LXXLL motif. Applicants submit that the above examples show that binding of peptides can be used to demonstrate agonist activity. Applicants submit that a considerable amount of

experimental work has been carried out with respect to the presently claimed invention.

In response, it is not controverted that the description in the Examples all relate to the single species, estrogen. What is at issue is whether applicants are in possession of the huge scope of the genus claimed at the time of filing. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure indicates that the applicants have invented species sufficient to constitute the gen[us]. Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004).

To satisfy a written description requirement for a claimed genus a sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406. A representative number of species means that the species, which are adequately described, are representative of the entire genus.

As applicants stated above, the specification provides a definition and lists of the numerous undefined components of the method. A listing (or definition) of every possible test compound, reference compound and other undefined components does not constitute a written description of every species in a genus. It would not reasonably lead those skilled in the art to any particular species. In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

Applicants submit that the Valadon reference solves the problems associated with hexapeptide binding. Valadon shows that in 1996 it was known that hexa- and decapeptide motifs could be identified using phage display libraries. In contrast to the Examiner's statement, the Applicants believe the Valadon reference confirms that such libraries could be produced and used by a person of ordinary skill as the reference does refer to some problems with the short insert in the art. Even though the flanking regions appear to mask the hexapeptide, it is still clear that it is possible to identify hexamer libraries. Applicants further submit that Oliphant was published in 1987 and relates to using recombinant DNA libraries to look for the consensus sequences for E.coli promoters. While the success rate was about 1 out of 5 clones with some apparent interference

from flanking regions, the paper still shows the method was working. Moreover, Oliphant actually acknowledges that the technique is not difficult (pages 181-182) and suggests ways to improve the success rate. Applicants submit that Oliphant clearly teaches the skilled person how to address unexpected problems in this technology and reassure the skilled success.

In reply, as stated by applicants Valadon solves the problems associated with species of the hexa and decapeptide. Valadon does not allude to solving problems related to any or all types of peptides by identifying said hexa and decapeptide, specifically by phage display. There is nothing in Valadon that extrapolates or predicts the results of the hexa and decapeptide to any type of peptide, especially for peptides of no definite structure as in the claims. The claims do not define any specificity as to the type of receptor, reference compounds, test compound and other undefined variables of the genus claim.

Oliphant, like Valadon, describes the working method specific to rDNA libraries to identify (not predict) for the consensus sequences for the E. coli promoters.

Applicants need not guarantee the success of the full scope of the claimed invention. However, skilled artisans are provided with little assurance of success for the huge scope of the genus claim. See University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003). A written description of an invention involving a chemical ***genus***, like a description of a chemical species, requires a precise definition, such as by structure, formula [or] chemical name of the claimed subject matter sufficient to distinguish it from other materials. University of California v. Eli Lilly and Col, 43 USPQ 2d 1398, 1405(1997), quoting Fiers V. Revel, 25 USPQ 2d 1601m 16106 (Fed. Cir. 1993). It is not sufficient to define it solely by its principal biological property, . . . because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property.

Claim Rejections - 35 USC § 112, second paragraph

New claims 135-157 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point

out and distinctly claim the subject matter which applicant regards as the invention.

A). Claim 136 is unclear as to what constitutes a panel-based descriptor, especially in the absence of positive definition or recitation in the specification.

B). There is no definition for Xaa in claim 148.

Double Patenting

New claims 135-157 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 6 of U.S. Patent No. 6,617,114 ('114 Patent) for reasons set forth in the last Office action.

Response to Arguments

Applicants submit that the '114 patent claims a method to identify ligands which can mediate the biological activity of a target protein via inhibition of the binding of a target protein to a binding partner ligand. In step (a) of claim 1 of the '114 patent, a first combinatorial library is screened to identify ligands that inhibit the binding of target-binding peptides. In contrast, claim 135 of the present invention now recites forming a reference fingerprint from panel members (usually peptides) and known modulators of the biological activity of receptor (step 1), forming a test fingerprint from an unknown

compound (usually a suspected agonist or antagonist of the receptor) and the same panel members and comparing the test fingerprint and the reference fingerprint predict the receptor modulating activity of the test compound (step 3). Applicants submit that the invention claimed in the present application is clearly distinguishable from the invention claimed in the '114 patent. The '114 patent does not claim forming a test fingerprint as explicitly recited in the claims of the present invention. The '114 patent does not claim forming a reference fingerprint using a test substance as explicitly recited in the claims of the present application. Moreover, the '114 patent does not claim any type of comparison between a reference fingerprint and a test fingerprint. On this basis, Applicants submit that clearly there is an embodiment of the present invention that falls outside the scope of the claims of the '114 patent.

In reply, is this merely a matter of semantics? The '114 patent discloses identifying, which in essence is the present method of predicting. It is not clear as to the essentiality of merely predicting a test compound modulating activity. Read in the light of the specification and as known in the art, screening results in the identification of a compound with an activity. One cannot predict, especially in a highly

unpredictable art, as biotechnology, a modulating effect of a compound. Rather, one identifies a modulator. Furthermore, fingerprinting is nothing more than identifying the compound i.e., characterizing the compound by its activity or structure. It is well known in the art that test compounds are normally compare with a reference or standard compound in order to compare and verify, a test compound relative to a known, reference compound. (See the original claims.) Hence, it would be within the ordinary skill in the art at the time the invention was made to compare the test compound identified in the '114 patent to determine whether in fact the test compound exhibits modulating activity relative to a the reference modulating activity. Comparative assay is one of the known assay employ in the art.

Claims 135-159 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-29, 32, 35 and 37 of the copending Application Nos. and 10/346,162 for reasons advanced in the last Office action.

Response to Arguments

Applicants will submit a suitable Terminal Disclaimer upon indication of allowable subject matter in the present application.

In response, in the absence of a terminal disclaimer, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 135-139, 142-146 and 156, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauvar(USP 5,587,293).

Kauvar discloses at col. 2, line 60 up to col. 3, line 60 a method comprising preparing a reactivity binding profile of the target receptor with respect to a "training set" of compounds (plurality of members in a panel, as claimed), preferably having characteristics which are systematically diverse. The training

set might include, for example, ten different compounds, which will have varying degrees of affinity for the target receptor. Thus, the target receptor profile will show a set of varying affinities with these compounds. Rather than test additional candidate ligands with respect to the target receptor itself, a "surrogate" is artificially created by testing the reactivity of this same set of ten training compounds against another panel to which the training set also shows varying degrees of reactivity. This might be called a reference receptor panel. Each compound in the training set will therefore show a pattern of reactivities with respect to this second panel. This results in a two-dimensional matrix wherein the level of reactivity of each member of the training set with respect to each member of the receptor panel is recorded. The level of reactivity of each member of the reference panel with each of the training compounds is thus simultaneously recorded in an orthogonal dimension. Each one of the "reference receptors" will show a different profile with respect to the training set than did the actual target receptor. However, some computational combination, preferably a linear combination, of the these reference receptor profiles will generate a profile which matches as closely as possible that obtained from the target receptor itself. That optimal approximation constitutes a surrogate for the target

receptor. The formula, which results from the computation with respect to the reference receptors is used to estimate reactivities for newly tested compounds. Empirically, such surrogates have good predictive power when applied to ligands outside the training set. A library of ligand profiles against the reference panel can thus be searched computationally with results comparable to a direct physical screen of the ligands. Thus, for each compound subsequently tested, reactivity against each member of the reference panel is obtained and the formula derived from the training set is applied to obtain a predicted value with respect to the target receptor. Rather than directly testing the reactivity of a candidate compound with a target, it is possible instead to test its reactivity with respect to a panel of readily available reference receptors, apply the formula to the results, and predict what would have happened had the target receptor itself been used. The larger the library of stored ligand profiles against a reference set, the larger the increase in efficiency for screening by surrogate. Accordingly, the claimed method reciting broadly any kind of receptor and receptor-modulating compound is obvious over the teachings of Kauvar.

Response to Arguments

Applicants state that the present invention as recited in new claim 135 requires that the same receptor be assayed in a plurality of different conformations with different reference substances to produce different fingerprint for each substance. Applicants submit that Kauvar differ from the present invention in that Kauvar use different reference receptors (isozymes exemplified in Example and at col. lines 46-67) each in a single conformation, whereas the current invention requires that the same receptor be assayed in a plurality of different substances conformations with different reference substances.

In reply, the suggested teaching of Kauvar that "….rather than directly testing the reactivity of a candidate compound with a target, it is possible instead to test its reactivity with respect to a panel of readily available reference receptors, apply the formula to the results, and predict what would have happened had the target receptor itself been used…."

Thus, Kauvar at least suggests the use of the same receptor.

Claims 140-141, 147-155 and 157, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Kauvar in view of Kushner et al (USP 5,723,291) or Yang et al (5,445,941).

Kauvar does not disclose the receptor as a nuclear receptor i.e., estrogen. However, Kushner discloses at col. 5, lines 33-35 that estrogen receptors activate transcription by interaction with another response element, the AP i binding site, instead of binding to EREs. This AP1 mediated pathway, referred to as the indirect estrogen response, may account for much of the agonistic properties of tamoxifen and other putative antiestrogens. Yang discloses at col. 2, line 38 up to col. 3, line 35 a method of screening for antiestrogens. In general, antiestrogens inhibit (antagonize) the activity of estrogen in the body. Antiestrogens bind to the estrogen receptor, although it is believed that the interaction between antiestrogens and the estrogen receptor involves a different domain of the receptor than that to which estrogen binds. Some antiestrogens, on the other hand, display pharmacological properties that are a mixture of agonist and antagonist properties. In other words, these compounds cause certain effects that mimic estrogen, while antagonizing other effects that are commonly associated with estrogen administration in cells that express the receptor. Because of this mixed effect of some antiestrogens, they are

subject to the same adverse effects associated with estrogen replacement therapy. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use estrogen receptor in the method of Kauvar as taught by Kushner or Yang. The advantages derived in identifying or obtaining anti-estrogen for use in therapeutics would provide the motivation to one having ordinary skill in the art to use as test compounds estrogen.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated

from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0812. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
June 13, 2005